Metabolism and Pathophysiology of Bariatric Surgery
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Foreword

Having trained and worked in two of the largest bariatric centers in the United Kingdom (King’s College Hospital NHS Foundation Trust and Imperial Healthcare NHS Trust, London), within both clinical and academic settings, I fully appreciate the enormity of the challenge obesity poses to health care systems.

The World Health Organization (WHO) estimated that globally, in 2014, more than 1.9 billion adults were overweight and more than half a billion were obese. The prevalence more than doubled between 1980 and 2014. Obesity, which was once associated only with high-income countries, is now also prevalent in low- and middle-income countries as well. Furthermore, overweight children are likely to become obese adults, thus, childhood obesity and overweight is one of the most serious public health challenges of the 21st century. Obesity and overweight can have a variety of adverse health consequences and metabolic effects associated with a high rate of death, such as type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, steatohepatitis, and certain types of cancer. It is estimated that around 65% of the world’s population lives in a country where overweight and obesity kills more people than underweight.

The huge economic burden to the health systems across the world highlights the importance of collectively addressing this global epidemic. Currently, bariatric (weight loss) surgery has become the only long-term effective treatment for severe (morbid) obesity, as calorie-restricted diets and drug therapy have had disappointing results for weight loss. Remarkably, bariatric surgery not only helps to achieve significant and sustained weight loss, but also leads to multiple metabolic benefits. Thus, the consensus among experts in the field is to refer to bariatric surgery as “metabolic surgery.” Over the past decade, there has been a significant global rise in basic science and translational research studies looking into the pathophysiology of bariatric surgery, which potentially holds the key to the long-term management of this epidemic. With all its merits in contributing to metabolic improvements, bariatric surgery is also associated with complications that can be devastating if not managed appropriately in well-established bariatric centers of excellence.

This book, “Pathophysiology of Bariatric Surgery: Metabolism, Nutrition Procedures, Outcomes, and Adverse Effects,” takes the reader on a journey through the complex world of obesity, highlighting that there is more to obesity than excess weight or an expanding waistline. The authors provide an in-depth review of how weight contributes to obesity-related comorbidities, and the rationale behind the different surgical procedures used. There is also comprehensive insight into the nutritional and metabolic complications, as well as the much-neglected psychological and behavioral aspects, of obesity before and after bariatric surgery. Ideally, the intended audience will appreciate and relate to the multiple challenges faced by obese patients in dealing with their physical and mental health issues as they weigh the favorable results and adverse outcomes of bariatric surgery. Ultimately, it is a life-changing surgical intervention that leads to either euphoria or despair.

The content of this book is relevant and current to my own clinical practice and obesity-related research, which makes it a timely publication. It is intended to be both informative and easy to read as an important reference for clinicians, allied health professionals, students, and all those interested in the complexity and management of obesity.

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Preface

In the United States, about one-third of the population are obese. While no state in the United States has an incidence less than 20%, in some communities, 50% of the adult population may be obese. The adverse effects of obesity include increased cancer rates, metabolic syndrome and diabetes, heart disease, stroke, sleep apnea, liver disease, musculoskeletal problems, and various psychological changes. Thus, obesity can be considered a disease that affects not only the individual, but the family unit, the local community, and the nation as a whole. For example, the medical cost of obesity in the United States alone is $150 billion annually.

There are various strategies to reduce obesity. These include dietary changes, behavioral modifications (including exercise), and drugs (that can cause malabsorption or alterations in satiety—appetite signaling). However, they are not always effective, and at that stage bariatric surgery becomes a viable alternative.

Bariatric surgery has been shown to improve numerous psychological, metabolic, physiological, and functional parameters. These include quality of life measures, diabetes, hypertension, hyperlipidemia, and sleep apnea. However, there are different types of bariatric surgery, including Roux-en-Y gastric bypass (RYGB), gastric banding, sleeve gastrectomy (SG), biliopancreatic diversion (BPD), and other variations of these procedures. The various weight loss procedures have different levels of popularity, outcomes, and success rates. Their effects on reducing obesity and comorbidities are dissimilar as well. Dissimilar bariatric procedures also have variable cellular and tissue effects, as well as nutritional complications. It is therefore clear that there are complex interrelationships between obesity and metabolic profiles before and after bariatric surgery. However, understanding these relationships has been difficult as the information relating to nutrition, surgical procedures, outcomes, and side effects have never been marshaled into a single text. *Pathophysiology of Bariatric Surgery* addresses this in a comprehensive way.

The book has eight sections:
1. Features of Obesity and Strategies for Weight Loss
2. Surgical and Postsurgical Procedures
3. Safety and Outcomes
4. Metabolism, Endocrinology, and Organ Systems
5. Nutritional Aspects
6. Cardiovascular, Body Composition, and Physiological Aspects
7. Psychological and Behavioral Aspects
8. Resources

The Editors recognize the difficulties in assigning some chapters to different sections. Very often chapters cover different scientific domains, and they could equally fit into one of several sections of the book. However, this is resolved by the excellent indexing system compiled by Elsevier.

Novel features in each chapter include a *Mini-Dictionary of Terms, Key Facts, and Summary Points.*

Contributors are authors of international and national standing, leaders in the field, and trendsetters. The emerging fields of obesity and bariatric surgery, as well as important discoveries relating to diet and nutritional health, are also incorporated in *Pathophysiology of Bariatric Surgery.* This represents essential reading for nutritionists, dietitians, surgeons, health care professionals, research scientists, molecular and cellular biochemists, physicians, general practitioners, public health workers, and anyone interested in well-being in general.

*Editors*

Rajkumar Rajendram, Victor R. Preedy & Colin R. Martin
Chapter 1

Obesity and Cardiac Failure: Pathophysiology, Epidemiology, Clinical Manifestations, and Management

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LIST OF ABBREVIATIONS

- BMI: body mass index
- CO: cardiac output
- HF: heart failure
- HTN: systemic hypertension
- LV: left ventricular
- LVEF: left ventricular ejection fraction
- LVH: left ventricular hypertrophy
- RAAS: renin-angiotensin-aldosterone system

INTRODUCTION

The relation of obesity to heart disease has been a subject of interest since ancient times, but has been studied most extensively during the past half century [1–7]. Obesity affects the heart in multiple ways. However, the most intense focus, as it relates to bariatric surgery, has been on the impact of obesity on cardiac performance and morphology and its relation to heart failure (HF) [3–7]. The purpose of this chapter is to explore these issues.

CLASSIFICATION OF OBESITY

The World Health Organization classifies body weight on the basis of body mass index (BMI). Table 1.1 summarizes the current and proposed body weight classifications. For purposes of this review, the term severe obesity will refer to BMI ≥ 40.0 kg/m². Central obesity is commonly defined as waist circumference >102 cm in men and >88 cm in women, or waist–hip ratio >1.0 in men and ≥ 0.8 in women.

CARDIAC PERFORMANCE AND MORPHOLOGY IN OBESITY

Obesity causes changes in cardiac performance that may produce alterations in cardiac morphology and impairment of ventricular function in adults. Such maladaptation is most pronounced in severely obese persons, but may occur to a lesser extent in overweight, class I or class II obese patients [1,3–45]. These alterations in cardiac structure and function have also been reported in obese children and adolescents [1,3–5]. The following comments on the effects of obesity on cardiac performance and morphology apply primarily to severe obesity.
Altered Hemodynamics Associated With Obesity

Obesity, particularly severe obesity, is a high cardiac output (CO) state [1,3–15]. It was originally thought that elevated CO in obese individuals resulted exclusively from excess adipose accumulation. However, increased fat mass alone does not completely account for the increase in cardiac CO. Recent studies indicate that fat-free mass contributes to augmentation of CO, possibly to a greater extent than fat mass [1,4,5,7]. The rise in CO is accompanied by a decrease in systemic vascular resistance [3–5,7,10]. Heart rate in obese persons is reportedly similar to or slightly higher than that of normal weight individuals. Thus, increased left ventricular (LV) stroke volume is the predominant cause of increased CO [3–10]. LV dP/dt was normal and LV V_\text{max} was lower than predicted for lean patients in one study of class II–III obese subjects [11]. Myocardial oxygen consumption was greater than predicted for normal weight patients in the same study [11]. LV end-diastolic pressure and pulmonary capillary wedge pressure at rest are commonly, but not invariably, elevated at rest in severely obese patients [1–5,7,8–10–15]. Pulmonary artery pressure may be elevated in severely obese persons due to left HF, obstructive sleep apnea, and obesity hypoventilation [1–5,8–13]. In such individuals, right ventricular end-diastolic pressure and mean right atrial pressure may be elevated [1–5,8–13]. Pulmonary vascular resistance is often increased in severely obese persons due to pulmonary arterial hypertension from sleep apnea/obesity hypoventilation and/or from pulmonary arterial vasoconstriction in those with LV failure [1,3–5,7,8]. It is not uncommon to encounter a transpulmonary pressure gradient in severely obese patients [8].

Exercise substantially increases central blood volume and LV dP/dt in severely obese patients [1,3–5,8,14,15]. In a study by Kaltman and Goldring, LV end-diastolic pressure increased from 21 to 31 mmHg with aerobic exercise in severely obese patients [14,15]. At a workload three times that of the resting level, augmentation of CO is blunted in severely obese patients [8–10]. Arteriovenous oxygen difference, usually normal at rest, may become substantially elevated during exercise [8–10]. LV end-diastolic pressure rises out of proportion to stroke work in such individuals, indicating reduced LV compliance [8–10].

Changes in Cardiac Morphology Associated With Obesity

Smith and Willius reported autopsy findings in 135 obese individuals [15]. In most, heart weight was greater than that predicted for normal body weight. In nine normotensive patients who died of HF, there was no evidence of primary myocardial disease. The authors attributed increased heart weight to excess epicardial fat, an observation that was later disproved. Subsequently, three studies of postmortem findings in severely obese subjects, comprising a total of 33 patients,
reported LV hypertrophy (LVH) in all patients, and right ventricular hypertrophy in six patients [17–19]. Excess epicardial fat was present in 21 patients [17–19]. These studies included patients with systemic hypertension (HTN) and coronary artery disease. Thus, it is uncertain to what extent the pathology described is attributable to obesity.

In 1992, Kasper et al. published a study of 43 obese patients and 409 lean patients with HF [12]. Of those who underwent myocardial biopsy, a specific cause of HF was identified in 64.5% of lean subjects, but only 23.3% of obese subjects. The most common histologic abnormality in obese subjects was LVH. These findings lend credence to the existence of a “cardiomyopathy of obesity,” one that is characterized primarily by LVH.

A large number of studies employing noninvasive cardiac diagnostic techniques have compared cardiac morphology in obese and normal weight patients [3–5,7,20]. Nearly all of these studies have shown that LV mass is significantly greater in obese than in normal weight patients. This is certainly true for severely obese subjects, but has also been reported in patients with class I and class II obesity. LV wall thickness is commonly, but not always, increased in obesity. Several studies have shown a strong positive correlation between body weight indices and LV mass [3,4,20]. Some studies have shown a positive correlation between body weight indices and LV diastolic chamber dimension, but this observation is less consistent than the relation between body weight indices and LV mass [3,4,20].

A variety of factors may contribute to LVH development in obese persons [3–7,22–26]. HTN is perhaps the most common risk factor [3–7]. Elevated LV end-systolic wall stress has also been shown to contribute to LVH, even in the absence of HTN [22]. Duration of obesity is also an important predictor of LVH [24]. Volume overload due to obesity increases LV preload, which also contributes to the development of LVH [3,4,22]. Fat-free mass contributes to increased LV mass to a greater extent than fat mass [25]. Multiple neurohormonal and metabolic alterations commonly present with obesity have been associated with the development of LVH [3–5,26–28]. These include activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, hyperleptinemia associated with leptin resistance, and insulin-resistance with hyperinsulinemia [3–5,26–28]. Insulin-related growth factors have been associated with LVH in human and animal studies [3–5,7,27]. In addition, several studies of murine models of lipotoxicity have reported the presence of LVH [3–5,28].

Based on the hemodynamic alterations that occur with obesity (especially severe obesity), it was predicted that uncomplicated (normotensive) obesity would predispose a patient to eccentric LVH. Early studies appeared to support this hypothesis [20]. However, multiple studies have shown that concentric LV remodeling or concentric LVH occurs as frequently, and in some cases more frequently, than eccentric LVH in obese subjects whose LV geometry is abnormal [3–5,23,27–31]. Some studies showed a predominance of eccentric LVH in uncomplicated obesity [3,4,20,22,32,33]. Some of the studies showing a predominance of concentric LVH or concentric LV remodeling did not exclude patients with HTN, although one study adjusted for it [27]. None of these studies considered the relative duration or severity of obesity and hypertension. However, scrutiny of older studies suggests that concentric LVH or concentric LV remodeling was present to some degree in obese patients [3,4,20]. Possible explanations for concentric LVH or concentric LV remodeling in obese patients include the presence of HTN or pre-HTN, activation of the RAAS, increased sympathetic nervous system tone, the effects of growth factors associated with insulin-resistance and hyperinsulinemia, and failure to consider the relative duration and severity of obesity and HTN [3,4]. In addition, the definition of concentric LVH has changed. What used to be called “eccentric—concentric LVH” (commonly present in hypertensive obese patients) is currently classified as concentric LVH (Fig. 1.1).

**LV Diastolic Function in Obesity**

Hemodynamic studies of obese subjects have shown that LV filling pressure is frequently high in obese subjects [8,10–15]. Moreover, LV filling pressure may increase substantially during exercise due to reduced LV compliance [14,15]. This is particularly true in severely obese persons [14,15].

LV diastolic function in obese subjects has been extensively studied using the full array of noninvasive cardiac diagnostic techniques [3–5,7,35–38]. Multiple studies comparing LV diastolic function in normal weight and obese subjects have consistently shown LV diastolic filling or relaxation to be impaired in obese subjects relative to normal weight patients, regardless of the severity of obesity and regardless of the diagnostic technique used [3,4,35]. LV diastolic function becomes more impaired as the severity of obesity worsens. Pascual et al. noted abnormal LV diastolic filling in 12% of class I, 35% of class II, and 45% of class III obese patients using Doppler echocardiographic techniques [36]. Some studies have reported greater impairment of LV diastolic function to progressive increases in LV mass [3,4,34,35]. One study of severely obese subjects using Doppler echocardiography showed that impaired LV diastolic filling was present only in those with increased LV mass [34]. Others have described diastolic dysfunction in the
absence of LVH [3,4,33]. LV diastolic filling is more severely impaired with a longer duration of obesity [24]. Tissue Doppler imaging studies have shown reduced diastolic mitral annular velocities in obese subjects [37,38].

When considered in total, these studies suggest that LV diastolic dysfunction is common in obesity, and is particularly common in severe obesity. Most, but not all, studies relate this to increased LV mass. The results of tissue Doppler imaging suggest that diastolic dysfunction in obesity may in part be load independent. The degree to which neurohormonal and metabolic factors influence LV diastolic function in obesity apart from their effect on LV mass is uncertain. Several studies of murine models of lipotoxicity have described the presence of LV diastolic dysfunction [3–5,26].

**LV Systolic Function in Obesity**

LV systolic function, determined using LV ejection phase indices such as LV fractional shortening or LV ejection fraction (LVEF), has been less extensively studied than LV mass and LV diastolic function in obese patients [3–5,7,37–41]. In most obese subjects LV systolic function is normal or supranormal [3–5,7]. Comparison of LV ejection phase indices using noninvasive cardiac techniques have not consistently shown significant differences in obese and normal weight patients [3,4]. When LV systolic function is diminished in such patients, it is usually mildly reduced. The presence of moderate to severe LV systolic dysfunction should elicit an evaluation for comorbidities such as coronary heart disease that may produce such changes. Duration of obesity, severity of obesity, systolic blood pressure, and LV end-systolic wall stress have correlated negatively with LV ejection phase indices [3,4,24,39]. Recent studies using tissue Doppler imaging and LV speckle track imaging have shown decreased mitral annular velocities in systole and abnormal radial LV strain in obese (often asymptomatic) subjects with a normal LVEF [3,4,40,41]. This may indicate that LV systolic dysfunction is more common in obesity than was previously thought. Abnormal tissue Doppler imaging raises the question of whether there exists an intrinsic abnormality of LV systolic function in obese persons. Recently, adipokines including leptin, adiponectin, and resistin, and gut hormones such as glucagon-like peptide-1 and glucose-dependent insulintopic polypeptide, have been identified as possible mediators of LV systolic dysfunction in obesity [42]. In addition, some murine models of lipotoxicity have reported reduced LV fractional shortening [3–5,28].

**Right Ventricular Function in Obesity**

Right ventricular function has not been extensively studied in obese patients [41,43]. In the MESA-Right Ventricle Study, Chahal et al. reported a larger mean right ventricular end-diastolic volume, a larger mean right ventricular stroke volume, and a significantly lower mean right ventricular ejection fraction after adjustment for LV parameters [41]. Abnormal lateral tricuspid annular systolic and diastolic velocities on tissue Doppler imaging and abnormal circumferential and radial strain on speckle track imaging have also been described in obese subjects, possibly suggesting subclinical right ventricular dysfunction [43].

**Obesity and HTN: Effects on the Heart**

HTN is present in nearly 50% of class I and class II obese persons, and occurs in up to 60% of severely obese individuals [1–4]. The coexistence of obesity and HTN produces alterations in cardiac structure and function that differ somewhat from those associated with obesity and HTN alone [3,4,44–46]. To fully appreciate the relative contributions of obesity and HTN to cardiac structure and function in any individual, it is important to know the duration and severity of both.

With long-standing severe obesity and poorly controlled HTN, CO and stroke volume remain increased, but less so than in normotensive obese patients. LV stroke work is greater in obese hypertensives than in normotensive obese persons [8,44,45]. Systemic vascular resistance is higher in obese hypertensives than in normotensive obese subjects [3,4,8,44,45]. LV end-diastolic pressure is often elevated in obese hypertensives [3,4,8,44,45]. A hybrid form of LVH may occur in which LV wall thickness is greater and LV diastolic chamber size is less dilated than in normotensive obese patients [3,4,45]. Once called eccentric—concentric LVH, it is now classified as a form of concentric LVH. Left atrial enlargement occurs commonly in obesity HTN, and LV diastolic dysfunction occurs with high frequency [3,4,44]. LV systolic function usually remains normal [3,4,44].
HF AND OBESITY

Obesity is a risk factor for HF, and in severely obese individuals may serve as a primary cause of HF [1,3–5]. The changes in cardiac performance and morphology described previously predispose patients to HF in all classes of obesity, and in severely obese persons may be sufficient to serve as the primary pathophysiologic basis for HF [1,3–5].

Epidemiology

Kenchaiah et al. studied 5881 patients enrolled in the Framingham Heart Study and reported that 8.4% of those with class I and II obesity developed HF during a mean follow-up period of 14 years [47]. For every 1 kg/m² increase in BMI, there was an increase in risk of HF of 7% in women and 5% in men [47]. The risk of HF was significantly greater in overweight patients than in obese subjects [47]. Similarly, the risk of HF was significantly greater in obese than in overweight patients [47]. Alpert and colleagues reported that 24 of 74 class III obese subjects had clinical evidence of HF [48]. The prevalence of HF rose to 90% in those who were severely obese for more than 20 years [48]. A retrospective analysis of data from the National Health and Nutrition Examination Survey (NHANES-1) study also suggested that obesity serves as a risk factor for HF [49]. In a study of a low-risk Mediterranean outpatient population, obesity was identified as an independent risk factor for HF [50]. Obesity is also a risk factor for HF in hospitalized patients. In a study of more than 6000 inpatients discharged with a diagnosis of HF, Ow en et al. reported an incidence of obesity of 41.4% in patients with HF with a preserved LVEF and 35.5% in subjects with HF with a reduced LVEF [51].

The Obesity Paradox in Patients With HF

Although there is no question that HF is associated with reduced survival, there is increasing evidence of the presence of an obesity paradox in such patients with respect to mortality [3,4,6,52]. The paradox is that overweight and obese patients with HF live longer than normal weight patients with similar degrees of severity of HF. In a meta-analysis of 28,209 patients with HF reported by Oreopoulos et al., all-cause mortality was 16% lower in overweight patients and 33% lower in obese subjects with HF compared to normal weight patients [52]. A variety of studies have shown that underweight patients have higher mortality rates than normal weight or class I obese patients [3,4,6]. In some studies, mortality in class II obese patients is lower than in normal weight patients, but in other studies there is a trend toward higher mortality risk [3,4,6]. Mortality in class III obese patients has not been extensively studied or compared to other obesity classes. Limited data suggest that mortality risk in such patients is higher than that of normal weight, overweight, and class I and II obese patients, and is more comparable to that of underweight subjects [3,4,6]. Thus, it is likely that mortality risk in HF patients forms a “U” curve with respect to weight with the highest mortality rates in underweight and severely obese patients. The obesity paradox as it relates to HF appears to be applicable to a variety of populations including males and females, elderly and nonelderly patients, those with acute or chronic HF, patients with HF with preserved or reduced LVEF, and those with central and peripheral obesity. Possible explanations for the obesity paradox in patients with HF include greater metabolic reserves and less cachexia, greater muscle mass, better cardiorespiratory fitness, attenuation of the RAAS response, earlier diagnosis and more aggressive medical therapy in overweight and class I and II obese patients than in normal weight subjects [3,4,6].

OBESITY CARDIOMYOPATHY

Obesity cardiomyopathy can be defined as HF that is due predominantly or entirely to obesity [3–5,53]. Obesity cardiomyopathy occurs almost exclusively in severely obese patients [3,4,53]. To date, no unique cardiac structural or histologic abnormality has been consistently described in humans with obesity cardiomyopathy [3,4,54]. LVH is the most common structural abnormality encountered [3,4,54]. The hemodynamic and structural abnormalities described previously are noted in patients with obesity cardiomyopathy, except that alterations in cardiac performance and morphology are more pronounced in this syndrome than in asymptomatic obese persons [3,4,48,53]. The pathophysiology of obesity cardiomyopathy is summarized in Fig. 1.1.

Clinical Manifestations

Obesity cardiomyopathy is associated with symptoms and signs of HF, some of which are identical to those of other causes of HF and some of which are unique to severe obesity [3,4,53]. General symptoms and signs include dyspnea on exertion, paroxysmal nocturnal dyspnea, lower extremity edema (often brawny) weight gain, increased abdominal girth, jugular venous distension, pulmonary crackles, and gallop rhythm. Symptoms and signs that are more specific to severe
obesity include mental confusion and disorientation, somnolence, cyanosis, periodic breathing, subconjunctival suffusion, retinal venous congestion and papilledema, and in some cases sudden death. Cardiac murmurs are frequently absent. HF tends to be episodic and follows recent weight gain. Most patients have been severely obese for at least 10 years. Sleep apnea is present in up to 50% of patients, and obesity hypoventilation occurs in 10–20% [1,3,4,53].

Plasma natriuretic peptide levels are lower in obese patients than in lean patients with comparable degrees of severity of HF. In severely obese patients they may be up to 50% lower [3,4].

**Management of Obesity Cardiomyopathy: General Measures**

Exacerbations of HF are treated with sodium restriction, low-flow inspired oxygen, and loop diuretics [3,4]. With biventricular failure associated with bowel edema, intravenous loop diuretics are commonly used as initial therapy [3,4]. Drugs such as torsemide or bumetanide may be preferable to furosemide in such patients. If moderate to severe LV systolic dysfunction is present, then RAAS blockers should be considered [3,4]. Appropriate treatment of HTN should be provided. There are no specific antihypertensive drug regimens that are preferred, but angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly used as initial therapy [3,4,44]. Digoxin is used to help control the ventricular rate in patients with atrial fibrillation and in those with severe LV systolic dysfunction who remain symptomatic despite diuresis, beta-blockade, and RAAS blockade [3,4]. The role of beta-blockers, calcium
channel blockers, direct-acting vasodilators, and endothelin antagonists in obese hypertensives with normal LV systolic function without pulmonary hypertension is uncertain.

**Effect of Weight Loss on Cardiac Performance, Cardiac Morphology, and HF**

The most effective method for reversing alterations in cardiac performance and morphology in patients with obesity cardiomyopathy is substantial weight loss [3,4,7,42,54–61]. Bariatric surgery has been more effective than diet, exercise, and pharmacotherapy in achieving hemodynamic and structural changes, presumably due to the greater degree of weight reduction achieved using bariatric surgery techniques [1,3,5,42,54–61].

Multiple studies have demonstrated that substantial weight loss is capable of reducing total and central blood volume, CO, and stroke volume [3,4,13,54–57]. Systemic vascular resistance increases. LV end-diastolic pressure and pulmonary capillary wedge pressure do not consistently decrease following weight loss [3,4,14,54–57]. Whether right heart pressures decrease following weight loss depends on whether LV filling pressure decreases and whether sleep-disordered breathing improves [3,4]. Most studies assessing LV diastolic filling or relaxation after weight loss have shown an improvement, possibly related to regression of LVH [56,58]. The response of LV systolic function to substantial weight loss is variable. LV systolic function increased significantly in subjects with obesity cardiomyopathy and LV systolic dysfunction in one study [39]. When LV systolic function is due to comorbidities such as prior myocardial infarction, the response of LV function to weight reduction may be blunted [42].

Relatively few studies have assessed the effect of weight loss on HF symptoms and signs, functional capacity, and quality of life. Four small case series have demonstrated reversal of signs of HF, improvement in New York Heart Association functional class, reduction of dyspnea and edema, and improvement of quality of life with weight loss (predominantly from bariatric surgery) in severely obese patients with obesity cardiomyopathy [48,59–61]. A more extensive discussion of the effects of bariatric surgery on cardiac performance, morphology, and HF is presented in a later chapter.

**MINI-DICTIONARY OF TERMS**

- **Body mass index**: Body weight index calculated by dividing weight in kilograms by height in meters squared.
- **Heart failure**: Clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood (American Heart Association).
- **Cardiac output**: Product of LV stroke volume and heart rate.
- **Systemic vascular resistance**: Physiologic relationship of systemic pressure and flow calculated by dividing the difference between mean blood pressure and mean right atrial pressure by CO.
- **Systemic hypertension**: Blood pressure >140 mmHg systolic and/or >90 mmHg diastolic.
- **Severe obesity**: Defined herein as BMI ≥ 40 kg/m².
- **Left ventricular hypertrophy**: Increased LV mass.
- **Eccentric left ventricular hypertrophy**: Form of LVH characterized by a high LV radius-to-thickness or volume-to-mass ratio; usually caused by LV pressure overload states.
- **Concentric left ventricular hypertrophy**: Form of LVH characterized by increased wall thickness and a normal or reduced radius-to-thickness or volume-to-mass ratio; usually caused by LV pressure overload states.
- **Concentric left ventricular remodeling**: LV geometry similar to concentric LVH, but with LV mass insufficient to fulfill criteria for LVH.

**KEY FACTS**

- Obesity is a risk factor for the development of cardiac (heart) failure
- Obesity, particularly severe obesity, produces alterations in cardiac structure and function that predispose to heart failure
- Heart failure may occur in severely-obese individuals in the absence of other causes of heart disease
- Obesity cardiomyopathy is a term used to describe heart failure due predominantly or entirely to severe chronic obesity
- Overweight and mildly-obese persons with heart failure live longer than normal weight or underweight individuals with heart failure of comparable severity. This is known as the obesity paradox
- High blood pressure and sleep apnea occur commonly in obese persons and may cause changes in cardiac structure and function that make the development of heart failure more likely in obese individuals
- The most effective treatment for obesity cardiomyopathy is voluntary weight loss which may be accomplished by diet and exercise or bariatric surgery. Substantial weight loss is capable of reversing many of the abnormalities of cardiac structure and function as well as many of the clinical manifestations of obesity cardiomyopathy
Severe obesity produces hemodynamic alterations that predispose patients to changes in cardiac morphology, which may lead to impairment of ventricular function and subsequent HF.

- HF due predominantly or entirely to obesity is known as obesity cardiomyopathy.
- Various neurohormonal and metabolic factors may contribute to obesity cardiomyopathy.
- Obesity cardiomyopathy is predominantly characterized by LV failure.
- Pulmonary arterial hypertension due to left HF, sleep apnea, and obesity hypoventilation may lead to right HF in severely obese patients.
- Many of the pathophysiological and clinical alterations associated with obesity cardiomyopathy are reversible following substantial weight loss.

**REFERENCES**


Chapter 2

Obesity and Adipose Tissue Microvascular Dysfunction

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LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<td>CLS</td>
<td>crown-like structures</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>EAT</td>
<td>epicardial adipose tissue</td>
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<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
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<td>FFA</td>
<td>free fatty acids</td>
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<td>FMD</td>
<td>flow-mediated dilation</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PVAT</td>
<td>perivascular adipose tissue</td>
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<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-alpha</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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INTRODUCTION

Obesity has emerged as one of the most critical healthcare problems worldwide. Affecting both high- and low-income countries, nearly 2.2 billion people worldwide are currently overweight (BMI $\geq 25$ kg/m$^2$) or obese (BMI $\geq 30$ kg/m$^2$) [1]. Obesity prevalence in adults and children is continuing to rise, with significant short- and long-term health, social, and economic consequences [2]. Obesity is a strong predictor of all-cause mortality, and is closely linked to the development of several common medical conditions, including insulin resistance, type 2 diabetes mellitus, cancer, and cardiovascular disease. Premature heart disease and stroke are currently the major causes of death in this population [3]; thus, elucidating mechanisms of obesity-related vascular dysfunction are critical. Obesity is associated with a state of chronic systemic inflammation, and increasing evidence suggests that cardiovascular disease may be a consequence of adipose tissue dysregulation driven by an imbalance of pro- and anti-inflammatory adipokines and cytokines released from dysfunctional adipose tissues [4]. It is postulated that the adipose microenvironment may influence whole-body metabolic and vascular function through systemic release of adipocytokines that mediate pathophysiology in distant organs. A number of abnormalities can already be detected in the microvasculature within fat depots. The current chapter will describe these findings in the adipose milieu of obese humans that may have connections to systemic disease.

ADIPOSOPATHY IN OBESITY

Adiposopathy, or “sick fat,” is described as pathogenic adipose tissue changes that are associated with metabolic dysregulation and activation of proinflammatory pathways. While cardiometabolic risk generally increases as a function of
Adipose tissue volume (quantity), qualitative alterations that develop within fat tissues in obesity have also been linked to endocrine, metabolic, and immune perturbations that promote cardiometabolic disease [5]. Inflammation in fat is largely driven by nonadipocyte cell populations that infiltrate and reside in the stromal—vascular fraction of adipose tissue compartments. While numbers of T cells, B cells, neutrophils, and mast cells increase, macrophages are the most abundant immune cell in the adipose tissue of obese individuals [6,7]. Both animal models and clinical data have linked the extent of adipose inflammation to metabolic dysfunction such as insulin resistance. Adipose macrophages appear to exist in at least two different activated states characterized as M1 classically activated macrophages that produce proinflammatory cytokines linked to insulin resistance and atherosclerosis, and alternative M2 macrophages that are generally involved in immunosuppressive functions [4]. Both M1 and M2 macrophage populations have been described in human fat [8] and tend to aggregate around dying adipocytes forming distinct “crown-like structures” (CLS, Fig. 2.1). In clinical studies, obese subjects lacking CLS in their fat stores tend to exhibit reduced proinflammatory adipose gene expression and more favorable systemic cardiometabolic profiles compared to age- and BMI-matched individuals with evidence of CLS [9–11]. Cardiovascular disease may thus be the “collateral damage” of cytokine imbalances in adipose tissues that shape systemic phenotypes.

Adipose tissue dysfunction likely occurs in all fat depots under obesogenic stress, however clinical data suggest that visceral fat may be relatively more prone to dysfunction. Central adiposity and the deposition of intraabdominal visceral fat have been consistently linked with increased cardiovascular and metabolic disease risk, which may in part be related to upregulated synthesis and release of adipokines, cytokines, and lipolysis in these compartments. In contrast, the expansion of subcutaneous fat has been shown to be a lesser contributor, or in some cases even protective in the development of obesity-associated cardiometabolic dysfunction, although this latter concept remains controversial [12–14]. Individuals with a greater degree of visceral fat have higher circulating levels of free fatty acids, interleukin (IL)-6, C-reactive protein, and tumor necrosis factor (TNF)-α compared to individuals with peripheral obesity [15–18]. In addition, IL-6, vascular endothelial growth factor (VEGF), vasoconstrictor prostaglandins, plasminogen activator inhibitor-1, noncanonical wingless-related integration site (WNT)5A, and TNF-α are released in greater quantities from abdominal visceral compared to subcutaneous fat [8,15,19–21]. In contrast, levels of antiatherogenic adiponectin, omentin, and secreted frizzled-related protein (SFRP)5 are reduced in an obesogenic environment [4,19]. Mediators produced by adipose tissue that have been implicated in cardiovascular disease mechanisms are listed in Table 2.1, and also reviewed extensively elsewhere [4].

Epicardial adipose tissue (EAT) is also emerging as a potential candidate regulator of cardiovascular function given its close anatomic proximity to the coronary vasculature and myocardium, and shared microcirculation. EAT has been viewed as the “visceral fat depot” of the heart [22] and shares embryologic origin with intraabdominal fat. EAT volume has been identified as an independent predictor of cardiovascular disease risk in population-based studies [22,23]. Epicardial fat measured by different methods including echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) is postulated to influence cardiovascular risk through a number of mechanisms, including its role as a reservoir for free fatty acids and inflammatory mediators. However, the clinical implications of EAT are not yet fully understood, and further research is needed to clarify its role in the pathogenesis of cardiovascular disease.

**FIGURE 2.1** Histological illustration of inflamed human adipose tissue as demonstrated by light microscopy. As a hallmark of local chronic inflammation in human adipose tissue, CD68+ macrophages organize into “crown-like structures” (CLS, brown color [dark gray in print versions]) that encircle necrotic adipocytes. (A) 10× power; (B) 20× power, dotted arrows identify adipocytes and solid arrows indicate CD68+ macrophages.
Epicardial fat in coronary artery disease (CAD) patients displays greater infiltration of macrophages with M1 polarization and cytokine production consistent with a proinflammatory phenotype compared to non-CAD patients [25,26]. While the literature suggests that EAT has capacity for production of proinflammatory mediators with paracrine effects that may mediate cardiovascular disease [22], the relation of epicardial fat to atherosclerosis remains associational and future studies may usher in causal relationships.

**ADIPOSE TISSUE MICROVASCULAR DYSFUNCTION**

Blood vessels are lined by an endothelial layer in direct contact with circulating blood that is essential in maintaining and regulating arterial tone, local blood flow, inflammation, and thrombosis. It also plays a key role in nutrient

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<th>TABLE 2.1 Mediators Produced From Dysfunctional Adipose Tissue Implicated in Cardiometabolic Disease</th>
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<tr>
<td>Angiopoietin-like 4 (ANGPTL-4)</td>
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<td>Angiotensinogen</td>
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<td>Apelin</td>
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<td>C-reactive protein (CRP)</td>
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<td>Chemokine (C–C motif) ligand-5 (CCL-5)</td>
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<td>Free fatty acids (FFA)</td>
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<td>Intercellular adhesion molecule-1 (ICAM-1)</td>
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<td>Interleukin-1β (IL-1β)</td>
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<td>Interleukin-18 (IL-18)</td>
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<td>JNK</td>
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<td>Leptin</td>
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<td>Matrix metalloproteinase</td>
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<td>Monocyte chemotactic protein-1 (MCP-1)</td>
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<td>Nuclear factor kappa B (NF-κB)</td>
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<td>Plasminogen activator inhibitor-1 (PAI-1)</td>
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<td>Prostaglandins</td>
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<td>P-selectin</td>
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<td>Retinol binding protein 4 (RBP-4)</td>
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<td>Resistin</td>
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<td>Serum amyloid A (SAA)</td>
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<td>Toll-like receptor-4 (TLR-4)</td>
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<td>Tumor necrosis factor-alpha (TNF-α)</td>
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<td>Vascular cell adhesion molecule-1 (VCAM-1)</td>
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<td>Vascular endothelial growth factor- A165 (VEGF-A165)</td>
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<tr>
<td>Visfatin</td>
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<td>WNT5A</td>
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Adipose-derived mediators implicated in cardiovascular disease are listed in alphabetical order.
exchange in metabolic tissues such as fat, and can grow to meet the blood supply demands of expanding adipose tissue. The term “endothelial dysfunction” describes a pathophysiological state that is characterized by a loss of vascular homeostatic properties that promotes a vasoconstrictive, prothrombotic, proatherogenic, and antiangiogenic environment [27]. Endothelial dysfunction represents the earliest stage of the atherosclerotic process and severity of dysfunction in both coronary and peripheral vessels has been shown to independently predict future cardiovascular events [27]. As will be discussed, endothelial dysfunction can be detected in adipose tissue microvessels likely as a consequence of proatherogenic mediators released from dysfunctional fat. While degree of obesity has been linked to endothelial dysfunction such as impaired brachial artery flow-mediated dilation (FMD) [27,28], emerging clinical data make a compelling case that qualitative features of adipose tissue are also instrumental in shaping cardiovascular risk independent of total adiposity burden [29,30].

Adipose tissue qualitative features can be assessed noninvasively using CT attenuation, which utilizes a quantitative radiodensity scale measured as Hounsfield units. Radiodensity attenuation of fat is linked to insulin resistance, cardiac risk factors, and all-cause mortality, independent of total fat volume [29–33]. Animal studies suggest that lower radiodensity may be associated with higher lipid content, fibrosis, and inflammation, which have been linked to insulin resistance and endothelial dysfunction [31]. However, direct clinical interpretation of CT findings is limited because pathological tissue validation is largely lacking in humans. As such, histological adipose tissue inflammation has been shown to be significantly associated with vascular dysfunction in severely obese subjects [9,11]. While noninvasive imaging provides some perspective regarding adipose tissue quantity and “quality,” their relationship to vascular dysfunction tends to be primarily associational, and limited information is available regarding causal mechanisms with regard to how adipose tissue may directly cause vascular disease.

To address this issue, experimental approaches utilizing videomicroscopy or myography have been developed for studying adipose tissue arterioles and directly probe pathophysiology in intact segments of human blood vessels that can be removed from living subjects during bariatric surgery. This methodology can be utilized to gain insight into pathways that are differentially altered in disease conditions [8,20,34–46]. Given the systemic nature of endothelial dysfunction, the technique represents a pragmatic approach to studying vascular pathophysiology with potential translation to mechanisms relevant to systemic vessels. The method involves removal of fresh adipose tissue from visceral or subcutaneous fat depots that can be harvested intraoperatively by the surgeon during bariatric surgery or via minimally invasive percutaneous needle biopsy of subcutaneous fat. Adipose arterioles (75–250 μm internal diameter) are carefully isolated from surrounding fat, cannulated between two glass capillary pipettes in a heated organ bath, and perfused under physiological conditions. The organ chamber is attached to a video microscope that allows for the quantification of the adipose vascular diameter in response to various chemical and physical stimuli. A representative image of a cannulated adipose microvessel is displayed in Fig. 2.2.

Utilization of ex vivo microvascular studies has provided insight into potential pathologic connections between adiposopathy and the local microvasculature. In experiments that examined paired subcutaneous and intraabdominal visceral adipose tissue samples collected from severely obese (BMI ≥ 40 kg/m²) subjects during bariatric surgery, endothelium-dependent, acetylcholine-mediated vasodilation was significantly impaired in visceral compared to subcutaneous adipose tissue arterioles [8,45]. Studying paired depots from the same person removes the confounding effect of patient differences in systemic metabolic parameters and yields depot-specific signatures with evidence of profound dysfunction in the visceral milieu. The degree of vasomotor impairment is consistent across several endothelium-dependent vasodilators, including bradykinin, shear stress, and insulin [8,45,46]. Additionally, impairment is specific to the state of obesity since arterioles isolated from visceral fat of lean subjects display preserved endothelium-dependent vasodilation [38,43,44]. Responses to endothelium-independent vasodilators such as sodium nitroprusside and papaverine are generally preserved, which suggest intact vascular smooth muscle cell responses and selective impairment primarily at the level of the endothelium in adipose microvessels [8,20,44,45]. Complementary studies in endothelial cells isolated from visceral fat demonstrate impairment in endothelial nitric oxide synthase (eNOS) phosphorylation at the activating site serine 1177, suggesting abnormalities in nitric oxide (NO) bioactivity as a significant contributing factor to obesity-related vascular dysfunction [20]. A significant correlation between phosphorylated-eNOS expression in visceral adipose endothelial cells and brachial arterial flow-mediated vasodilation has been reported, suggesting parallel abnormalities in adipose and systemic circulations [47].

While profound derangements in visceral fat have been emphasized, perturbations are also evident in the subcutaneous depot of obese subjects which display blunted endothelium-dependent vasodilation compared to subcutaneous arterioles in lean subjects. In fact, there appears to be a disease gradient with extreme microenvironmental abnormalities in the visceral fat of obese subjects, with lesser, yet still prominent, perturbations in their subcutaneous depots compared to lean subjects [37,38]. Even moderate obesity adversely impacts subcutaneous adipose microvascular endothelial
function, particularly in women [42]. The degree of vasomotor impairment is worsened when obesity is associated with diabetes, metabolic syndrome, or hypertension, and linked to systemic inflammation and decreased eNOS activity [36–38,42,48]. There are likely multiple mechanisms that lead to microvascular dysfunction in diseased fat. Adipose proinflammatory gene expression correlates negatively with acetylcholine-mediated arteriolar vasodilation [8], suggesting inflammation as an important factor. Arterioles and isolated endothelial cells isolated from the visceral depot of obese subjects display enhanced expression of proinflammatory mediators such as CCL-5, IL-6, JNK, TNF-α, and toll-like receptor-4 [8,43,44]. Moreover, vasomotor dysfunction is reversed following treatment with IL-6 and TNF-α antagonists [39,44]. Other pathogenic pathways involving oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress are also likely to contribute to adiposopathy and vascular diathesis. Adipose arterioles of type 2 diabetic obese subjects display impaired NO-dependent vasodilation along with abnormalities in mitochondrial structure and function [40]. Additionally, increasing telomerase activity in adipose arterioles of obese patients with CAD restores endothelial function by limiting vascular inflammation and mitochondrial reactive oxygen species production [34]. Systemic medications have direct effects on the adipose tissue microvasculature as treatment with a direct renin
inhibitor aliskiren or angiotensin-conversing enzyme inhibitor ramipril are associated with the correction of microvascular structural alterations [35]. Glucagon-like peptide 1 receptor agonists, in addition to improving glucose utilization, increase eNOS-mediated vasodilation in adipose arterioles via AMP-activated protein kinase activity in diabetic patients [41]. Lastly, the eicosanoid/cyclooxygenase pathway may also be important in obesity-linked vascular disease, as cyclooxygenase-mediated vasoconstrictor prostanoids appear to contribute to adipose microvascular dysfunction [20]. Collectively, as clinical data consistently link adiposity to cardiovascular risk, the ability to directly access and examine dysfunctional human blood vessels provides major opportunities to discover novel mechanisms that may have whole-body cardiometabolic implications.

Videomicroscopy and myograph culture methodologies are also used to examine the influence of perivascular adipose tissue (PVAT) on the microvasculature. Defined as fat that directly surrounds blood vessels, PVAT has the potential to elicit pathogenic signals upon the local microvasculature, analogous to epicardial fat. In healthy conditions, PVAT modulates vascular contractile tone by release of vasodilatory mediators, including NO and adiponectin, having an “anticontractile” effect [49]. Under obesogenic stress, however, PVAT loses its protective anticontractile phenotype, becoming pathogenic to the local vasculature most likely due to macrophage activation, oxidative stress, and inflammation [39,50]. Moreover, removal of presumably dysfunctional PVAT from arterioles of obese subjects restores endothelium-dependent vasodilation [43].

**ANGIOGENIC DYSFUNCTION IN OBESITY**

Generation of new blood vessels, termed angiogenesis, as adipose tissue expands with progressive obesity is important in maintaining metabolic and oxygen exchange, and consequently whole-body homeostasis. Experimental studies suggest that expanding adipocytes may outgrow their blood supply due to deficient tissue angiogenesis that may initiate localized ischemia, hypoxia, necrosis, and inflammation within the adipose microenvironment, which may lead to metabolic dysfunction [51]. As with the vasodilator functions described above, there is growing evidence that angiogenic properties of microvessels can exhibit abnormalities in human adipose depots. Clinical studies have examined angiogenic capacity in human adipose tissue using an *ex vivo* sprout assay [52,53]. As displayed in Fig. 2.3, different fat depots can exhibit varying angiogenic profiles quantified by capillary growth emanating from fat pads, confirmed by immunofluorescence. In human obesity, subcutaneous adipose tissue appears to display higher capillary density and angiogenic capacity compared to visceral fat despite paradoxical higher expression of proangiogenic factors such as

(A) Sprouts

(B) Fat Pad

**FIGURE 2.3** Assessment of adipose tissue angiogenic capacity *ex vivo*. Representative images of (A) normal and (B) blunted capillary growth from human fat pad explants after 7 days of culture.
VEGF-A [52,53] in the visceral depot. Among several mediators, proangiogenic angiopoietin-like 4 expression is down-regulated [52], while expression of antiangiogenic isoform VEGF-A\(_{165b}\) is increased in visceral fat and associated with impaired adipose tissue angiogenesis, which can be reversed upon targeted inhibition [53]. Capillary density and angiogenic potential of subcutaneous adipose tissue is blunted in severely obese compared to overweight individuals, which may have global cardiometabolic implications [52]. While vascularity and angiogenic features of fat may impact its metabolic functions, whether modulation of angiogenesis could influence clinical sequelae of obesity remains unknown.

WEIGHT LOSS AND ADIPOSE MICROVASCULAR FUNCTION

Bariatric surgery is currently the most effective and durable weight-loss intervention for obesity. The operation improves cardiac risk factors, remits diabetes, and to date represents the only clinical weight-loss intervention shown to improve long-term (>10 year) total and cardiovascular mortality by up to 50%, mainly from reduced myocardial infarction risk [54–58]. Meta-analysis of weight loss intervention studies show that systemic arterial endothelial function assessed by brachial artery FMD improves significantly following weight decline [59], and degree of vascular recovery may depend on subject characteristics or type of weight loss treatment. While mechanisms of benefit are incompletely understood, clinical data suggest that improved insulin sensitivity may be a dominant factor in cardiovascular risk reduction [58,60,61], and reversing systemic insulin resistance and endothelial dysfunction may be important clinical targets. At the adipose tissue level, weight loss has been shown to reduce ectopic fat burden and favorably remodel adipose tissue by attenuating macrophage-mediated inflammation [62–64]. Additionally, anticontractile functions of PVAT are restored following bariatric intervention and attributed to reduced inflammation and oxidative stress, and increased adiponectin and NO bioavailability [49]. Moreover, obesity-induced changes to the adipose microvascular structure also improve following bariatric surgical weight loss [65]. While bariatric surgery saves lives, it is obviously not an option for everyone, and ≤1% of eligible individuals undergo this procedure. However, by studying how the human vasculature favorably remodels following surgery, valuable physiological information can be learned and potentially translated for therapeutic applications.

CONCLUSIONS

With obesity rates on the rise worldwide, it will remain one of the most important global healthcare challenges for decades to come. A summary concept schematic illustrating local and systemic effects of obesity-induced adipose tissue dysfunction in promoting cardiometabolic disease is provided in Fig. 2.4. Endothelial dysfunction can be detected in adipose tissue arterioles of human subjects, and clinical studies have identified the dysfunctional adipose milieu and cytokine imbalance as contributors to vascular disease mechanisms. With clinical data consistently linking obesity to cardiovascular risk, examination of dysfunctional human blood vessels in adipose tissue domains may provide us with opportunities to discover novel translational clues to vascular disease mechanisms in human obesity.

MINI-DICTIONARY OF TERMS

- **Adipokines**: Adipose-derived mediators produced by fat cells.
- **Adiposopathy**: Pathogenic abnormalities that develop within fat tissue that lead to functional endocrine, metabolic, and immune changes that promote obesity-associated cardiometabolic disease.
- **Angiogenesis**: The generation of new blood vessels.
- **Central adiposity**: Preferential abdominal (vs peripheral) deposition of adipose tissue.
- **Endothelial dysfunction**: A pathophysiological state characterized by the loss of normal homeostatic properties of the vasculature that support a vasoconstrictive, prothrombotic, and proatherogenic environment leading to atherosclerosis.
- **Endothelium**: A single cell layer that lines the inside walls of blood vessels, important in maintaining and regulating arterial tone, blood flow, inflammation, and thrombosis.
- **Epicardial adipose tissue**: Fat that surrounds the heart.
- **Perivascular adipose tissue**: Fat that surrounds blood vessels.
- **Videomicroscopy**: An *ex vivo* method that measures the microvascular vasodilatory function of live arterioles.